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Review Article

The gastrointestinal microbiome in critical illness: A Clinician's guide to mechanisms, emerging tools, and therapeutic questions

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ABSTRACT

There is considerable interest in the gastrointestinal (GI) microbiome and its interaction with disease processes, but existing reviews tend to assume ecological and microbiological knowledge that critical care clinicians may not have. In this review, we present an overview of the GI microbiome for the critical care clinician and highlight unanswered questions pertinent to the field.

The human GI microbiome can now be mapped and its relationship with organ function interrogated. Multiomics approaches that integrate data from multiple sources, including the microbiome, epigenome, transcriptome, metabolome, and proteome, offer promise in unravelling the hitherto inconsistent results of interventions to modify the microbiome, with a view to improving outcomes.

Resident microbes are implicated in local and systemic immune dysregulation during critical illness. While the mechanisms underlying relationships between the GI microbiome and organ function in health and disease remain incompletely understood, a byproduct of saccharolytic fermentation of dietary fibre in the colon, short-chain fatty acids (SCFAs), are a key modulator of these relationships. Pertinent to the use of prebiotic formulations in treating chronic disease and critical illness, are the comparatively unexplored bidirectional interactions between the microbiome and host. More observational and interventional data, using advanced laboratory techniques, are needed to understand if these are causal relationships.

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1. Introduction

Microbiota is the term used to define all *microbes* in a certain environment, such as the gastrointestinal (GI) *microbiota*".[1] The term microbiome is currently best defined as the ecological community of commensal, symbiotic, and pathogenic microorganisms,[2] plus their genomic elements in a particular environment,[3] and the products of the microbiota and the host environment[4].

This review will describe the literature pertaining to the GI microbiome in critical illness, focusing on focusing on mechanisms, emerging tools, and therapeutic questions. Microbiomes of other regions (such as the oral and respiratory tract) may be important to outcomes[5,6] but are beyond the scope of this review.

2. Methods

A literature search was conducted using keywords related to the GI microbiome (e.g. "phylogenetic profiling", "microbial genome", 16S, "microbial diversity", "bacterial diversity", "dysbiosis", "microbial composition", or "bacterial composition", "gut flora", "microbiota") and critical illness (e.g. "artificial respiration", "mechanical ventilation", "shock", "trauma", "intensive care", "critical care", "critical illness") and was limited to adult humans,

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the English language, and articles published after 2011. Details of search terms utilised for various sections of this review can be found in appendix 1.

3. Definitions

A glossary of terms[1,7] relating to the study of microbiota is summarised in Table 1. A few selected terms are further described here.

The metabolome refers to the total complement of small molecule (<1500 Da) metabolites found in association with the microbiome.[8] When experts refer to metabolomics, they refer to the study of these metabolites that are thought to influence the host metabolism extensively.[9] Examples of such metabolites are short-chain fatty acids (SCFAs), described below.

Microbiota are often described in terms of diversity (Figs. 1 and 2).[10]

Alpha diversity (Fig. 1) relates to the measure of distribution of richness and abundance of a microbial population. It applies to a single sample (within-sample diversity) and is akin to the summary statistic of a single population. Alpha diversity is quantified using indices of evenness (e.g. Simpson[11]), diversity (e.g. Shannon,[12] Simpson), or richness (e.g. Chao1[13]). These alpha diversity metrics reflect different weighted means between species; for example, the Shannon index represents the weighted mean of the natural logarithms of species proportions, where weights correspond to the relative abundances of each species in a community. Alpha diversity will depend on the measure used, in Fig. 1C, for example, it will be high if richness-focused measures are used, while measures incorporating evenness will give a moderate value (Shannon diversity index) or a low value (Simpson's index). These measures are described in detail elsewhere.[14,15]

Beta diversity (Fig. 2) is a measure of the similarity or dissimilarity of two microbial communities, e.g. between two organs (between-sample diversity). Beta diversity can be measured by taxa overlap, or quantified by Bray–Curtis dissimilarity, which is a statistic of dissimilarity of two ecological communities, with a value of zero representing no dissimilarity and one indicating no similarity. These measures do not estimate changes in abundance of specific taxa but can estimate the extent of compositional difference. UniFrac[16] and Aitchison distance[17] are examples of widely used metrics in microbiome science, the former takes phylogenetic information into account, and the latter handles the compositional nature of microbiome data.

4. Analysis of the microbiome

Evaluating the human microbiota used to be a slow, time consuming, and expensive process. It involved oxygen-free culture methods requiring specialised equipment. However, methodological advances in culture-independent analysis have resulted in easier, faster,[18] and cost-effective[19] characterisation of the microbiome compared to traditional culture media methods. The methods of microbiome analysis are summarised in Table 2.

Sanger sequencing, now also known as “first generation sequencing”, was the gold standard method for determining the nucleotide sequence of DNA until the early 2000s. It uses modified nucleotides that stop the DNA synthesis reaction at different positions to determine the DNA sequence. It can be used for small-scale projects (e.g. sequencing polymerase chain reaction [PCR] amplicons) as it is highly accurate. The major drawback of Sanger sequencing is that only a single sequencing reaction can be performed at a time, which limits throughput.

“Next-generation sequencing” followed. This method allows sequencing of millions of very short DNA fragments (typically <100 base pairs) in parallel.[20] It remains the default method for most sequencing projects (especially microbiome metagenomics). Next-generation sequencing was the driver for developing methods for sample barcoding (described later), bringing costs down and making microbiome sequencing more accessible. More recent next-generation sequencing technologies can read nucleic acid fragments much longer than earlier methods (e.g. PacBio and ONT platforms). These so-called “long-read” technologies[21,22] permit substantially higher resolution of genetic diversity in

Table 1
Glossary of terms specific to microbiota research.

General terms	
Metagenome	The collection of all genomes (individual genetic makeup) in a sample and encoded functions
Metatranscriptome	The collection of mRNAs of a metagenome and it's regulation and expression (a snapshot in time)
Metaproteomics	The large-scale study of the entire protein collection of a specific sample at a given point in time, using mass spectrometry, and linking genotype to phenotype
Metabolomics	The study of metabolites expressed by an organism, cell or tissue
Metabonomics	The change in the metabolome in a sample over time or in response to a stimulus (e.g. antibiotics)
Descriptive ecological terms	
Abundance	The quantity of a given taxa in a sample in absolute or relative terms
Eveness	The relative abundance of different taxonomic groups. Species evenness measures how close in population size each species is in an environment, e.g. if there are 10^{10} *Bifidobacteria* and 10^{30} *Klebsiella*, the community is not very even. However, if there are 10^{10} *Bifidobacteria* and 10^{11} *Klebsiella*, the community is relatively even. Of note, dominance is the inverse of evenness.
Functional diversity	Variation of traits between organisms within an ecological unit.
Protist	A kingdom including predominantly eukaryotic, unicellular, microscopic organisms
Richness	The number of different bacterial taxa in a sample
Analytic terms	
Operational taxonomic units	Clusters of sequences (commonly 16S rRNA) that are similar and used to represent a taxonomic group as an estimation of the abundance, applied commonly to genus and occasionally at the species level (operational taxonomic units [OTUs])
Shannon index	Measures the diversity of species (species richness) but also considers the abundance of each species. Communities with a large number of species that are equally abundant have a higher Shannon index compared to those with the same number of species but dominated by few abundant members (lack of eveness). It is a measure of the degree of uncertainty in predicting the presence of a species in a random sample, with lower diversity meaning lower uncertainty and vice versa.
Chao index	Used to estimate the abundance of OTUs in a sample. A higher Chao index indicates a larger quantity of OTUs and therefore relatively higher species diversity. Chao1 is abundance-based chao 2 is incidence-based.
Shannon/Chao interpretation	High Chao1/low Shannon = high richness (esp. Rare taxa), uneven. Low Chao1/high Shannon = lower richness (esp. Rare taxa), more even.
Simpson index	Estimates the probability that two individuals randomly selected from a sample will belong to the same species, 0 indicating low and 1 indicating high diversity.

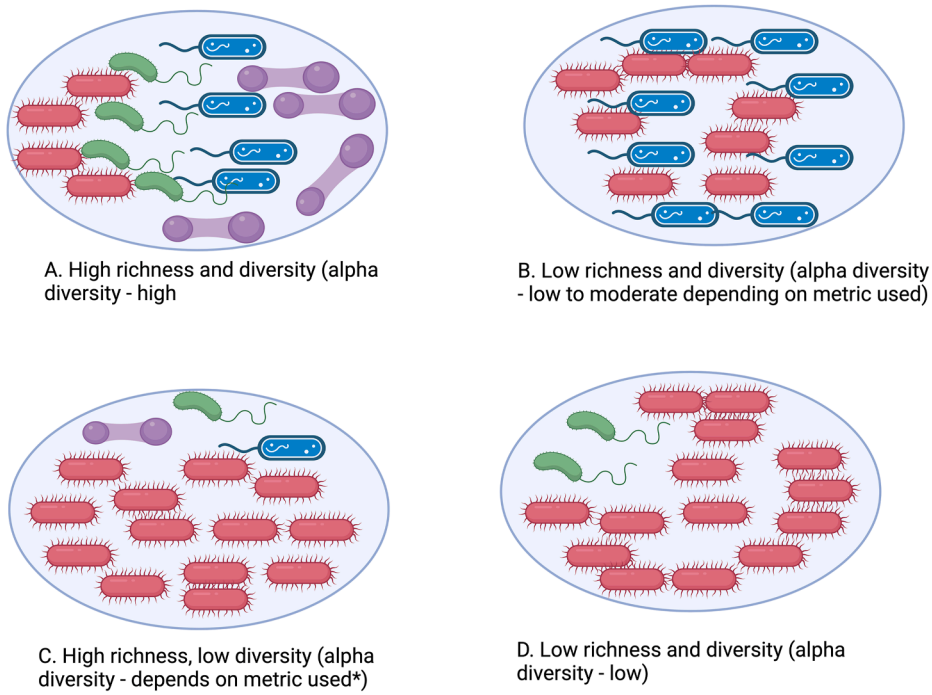
A. High richness and diversity (alpha diversity - high
B. Low richness and diversity (alpha diversity - low to moderate depending on metric used)
C. High richness, low diversity (alpha diversity - depends on metric used*)
D. Low richness and diversity (alpha diversity - low)

Fig. 1. Alpha diversity. Schematic diagram of richness and diversity. Each distinct bacterial taxon is represented schematically. Richness represents variety (e.g. number of species present). Diversity relates to preponderance of communities over others, where overrepresentation of one taxon reduces diversity. * See text for further explanation. Created in https://BioRender.com.

complex microbiomes. Long reads improve microbiome biodiversity assessments, identification of pathogens in clinical specimens and cultures, population biology, epidemiology, epigenetics, and metagenomics.[23] Cost, turnaround time, and ease of DNA sequencing library preparation are improving, thus making the technology increasingly attractive for use in clinical settings, including for routine microbiome assessments.

An array of computational methods exist for analysing data generated by culture-independent methods. It is useful to understand what information each method yields. For example, 16S rRNA sequencing attempts to answer the question, "Who is there?" Metagenomic shotgun sequencing attempts to answer, "Who is there and what can they do?" Metatranscriptomics attempts to answer, "Who is there and what are they doing?"[24]

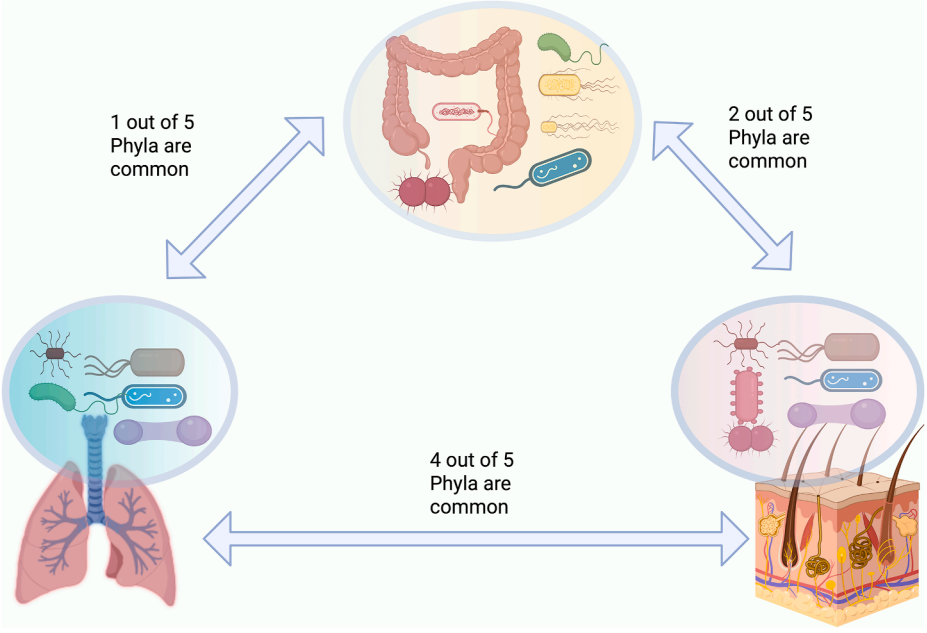

Fig. 2. Beta diversity. Schematic diagram explaining between-sample similarity. Here only one of five Phyla is shared between the colon and lungs, two out of five between colon and skin, and so forth. Created in https://BioRender.com.

Table 2
Microbe characterisation techniques.

Microbe characterization techniques					
Technique	Description	Resolution of Phylogeny	Advantages / drawbacks	Cost and efficiency	
Culture	Traditional method	Small number of known organisms grown	Gives additional information on antibiotic resistance and pathogenicity	Low throughput, 1 sample per media, takes 24-72 hrs, $	Low resolution of microbe community
PCR panels	RT-PCR, qPCR (marker gene analysis). Primers that target a specific region of a gene of interest are used to determine microbial taxa in a sample.	Depending on panel chosen usually includes around 20 known organisms per sample. Undiscovered taxa are missed by a targeted panel.	Provide absolute abundance of each taxon per gram or millilitre of sample. Useful for small and host DNA contaminated samples. Prone to bias as PCR cycle numbers increase, amplifying contaminants.	Low throughput, 30 samples per sequencing run, takes up to 5 hrs, $$	
Amplicon sequencing	Partial genomes found by amplifying and sequencing regions of highly conserved bacterial genes, which are then compared with an existing database to determine from which bacterial organisms the sequences came.	Most selected organisms present. Genus level resolution, not species	High yield from small samples. Simple data analysis relative to whole genome sequencing. The incorrect primer choice can result in highly erroneous results.	High throughput, 350 samples per run, 48 hrs, $$	
Metagenomic (“shotgun”) sequencing	The whole genome in a sample is cleaved randomly (hence “shot-gun”) into short DNA/RNA fragments and then the reads are compared (aligned) to reference databases to assign taxonomy and function	Every organism present will have genome sequenced with expanded taxonomic range and strain resolution	Includes fungal and viral information that may be missed by Amplicon sequencing. Can analyse with nanograms of sample. “Functional potential” is captured (what the microbes are *capable* of doing - but not whether they are actually doing it under the given condition)	High throughput, 384 samples per run, 48 hrs, $$$	
Metaproteomics	Protein made by all organisms in the sample	No link to specific organisms	Good for looking for functional changes	High throughput, 100-300 samples per run, 48 hrs, $$$$	
Metatranscriptomics	All RNA produced by organisms in the sample	No link to specific organisms	Good for looking for functional changes	High throughput, 100-300 samples per run, 48 hrs, $$$$	
Metabolomics	All small molecules (non-protein) made by organisms present	No link to specific organisms	Good for looking for functional changes	High throughput, 100-300 samples per run, 48 hrs, $$$	High resolution

While DNA and RNA sequencing methods are extremely powerful, they are not without biases and limitations. The range and magnitude of the biases differ between sample types and sequencing methods. As an example, taxonomic classification biases due to PCR primer selection are a major problem with 16S rRNA gene sequencing but not with shotgun metagenomics; host DNA contamination is a big issue with metagenomics but not with 16S rRNA gene sequencing; sample storage is extremely important in metatranscriptomics because messenger RNA (mRNA) is unstable. Therefore, use of a combination of methods is often recommended to account for the limitations of any one method.[25]

There are several technical steps with attendant risk of bias and error, which need consideration in choosing an appropriate method of DNA sequencing (Fig. 3). It is important to understand the risks and limitations of these methods when trying to interpret results of microbiome studies.

First, cells are lysed using physical or enzymatic methods, and nucleic acids (DNA, RNA, or both) are extracted by exploiting their negative charge. Next, nucleic acids are fragmented to an appropriate size for the sequencing platform (short reads or long reads), followed by preparation of the sequencing library. This involves attaching specific synthetic oligonucleotides (adaptors) to both ends of RNA/DNA fragments and, optionally, amplifying the repaired fragments if DNA concentration is low. Barcoding, an optional but commonly used step, tags each sample's sequencing library with a unique short DNA sequence to attribute data to its original sample. This enables pooling of multiple samples in a single sequencing run, reducing costs. Next, sequencing begins by loading libraries onto the chosen platform (e.g. Illumina, PacBio, or ONT). Finally, generated sequencing data are fed into a “pipeline” for analysis. In next-generation sequencing, a "pipeline" refers to a structured sequence of computational processes and tools used to analyse raw sequencing data and transform it into meaningful biological information.

5. The gastrointestinal microbiome in health

Our understanding of the function and interaction of the GI microbiome is predominantly extrapolated from animal models[26,27] and healthy human cohorts. The GI microbiome can be characterised as a dynamically acquired genome, as opposed to a stable inherited genome.[28] A person's microbiome is affected by a multitude of factors throughout life, including mode of birth, age, diet, illness, and treatments administered.

Humans are thought to be born with sterile GI tracts. Colonisation begins immediately after birth and changes throughout life with great intra-individual variability.[29,30] However, this view has been recently contested with the detection of bacterial DNA in previously so-called “sterile sites”.[31]

Mapping of the GI microbiota in health has been done.[32,33] In health the human GI microbiota consists of approximately 1500 bacterial species grouped into 50 phyla (the number identified continues to increase). However, approximately 93–94% of species belong to four main phyla; these are, in descending order of abundance, Firmicutes, Bacteroidota (formerly Bacteroidetes), Pseudomonadota, and Actinomycetota (formerly Actinobacteria)[34,35] It is important for clinicians to appreciate these categories because most trials and observational studies describe results in terms of these phyla (Table 3). There are contributions to the microbiota by viruses (notably bacteriophages) and mycobiota (fungal microbiota e.g. Candida and Saccharomyces), previously thought to be minor, but this view is increasingly challenged.[36–40]

6. The gastrointestinal microbiome in chronic diseases

The microbiome has been studied predominantly in healthy humans,[32,41,42] and the possible impact of microbiota on disease

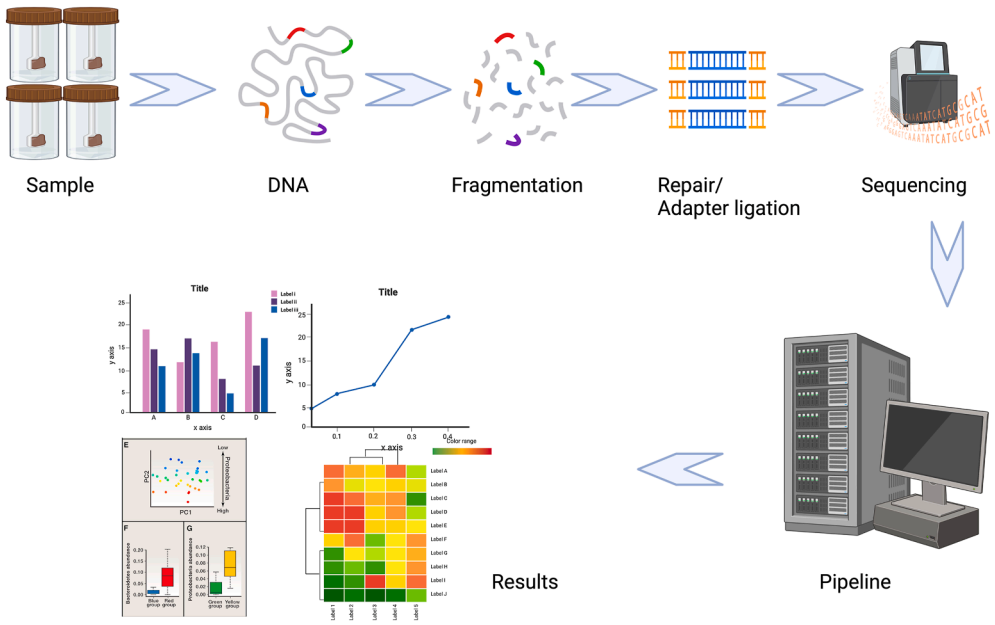

Fig. 3. Schematic diagram of the steps in analysis of the microbiome. Created in https://BioRender.com.

states has been explored. Chronic conditions such as asthma,[43–45] schizophrenia,[46–48] Alzheimer's disease,[49–51] obesity,[52–54] and type 1 diabetes[55–57] appear to exhibit characteristic microbiome changes. In the critical care setting, the GI microbiome has been most studied in newborns.[58–60] However, very little is known about the microbiome in adults with acute diseases that precipitate admission to an intensive care unit (ICU).

7. The gastrointestinal microbiome during critical illness

7.1. Dysbiosis during critical illness

Dysbiosis describes the disruption of the microbiome that may be harmful to the host. Disruption may involve reduced numbers or diversity of health promoting bacteria, or colonisation with pathogenic microbes.[61] However, a “normal” or “healthy” microbiome is challenging to define, as it can vary based on diet, geography, and ethnicity. Accordingly, dysbiosis is relative to an individual's own healthy microbiome. To accurately determine dysbiosis requires microbiome sampling from an individual before and after an event or intervention. Because samples have not been obtained prior to critical illness (except prior to elective major surgery), dysbiosis during critical illness usually refers to a loss of commensal bacterial diversity and enrichment with pathogenic species. GI dysbiosis is prevalent during critical illness.[62,63] This is due to the inflammatory response, driven by the acute illness or injury, and the treatment provided as part of critical care. Loss of diversity is observed both within sites (alpha) and between sites (beta), with colonisation by a single potentially pathogenic taxon (low beta diversity).[64,65] Dysbiosis and its effects are illustrated in Fig. 4.

7.2. Immune dysregulation associated with dysbiosis

GI dysbiosis is thought to contribute to subsequent immune dysregulation.[66–68] The link between dysbiosis and immune dysfunction is well established in experimental animal models,[69] but there is limited direct evidence from clinical trials. A post-hoc analysis of data from a small trial[70] randomising 25 recipients of haemopoetic cell transplant to autologous faecal microbial transplant or placebo reported an association between levels of circulating white blood cells and diversity of the GI microbiota.[71] Two sub-studies of the Human Functional Genomics Project suggested a complex and variable association between dysbiosis and cytokine production.[72,73] A prospective longitudinal cohort study of 51 mechanically ventilated patients reported an association between progressive Enterobacteriaceae enrichment and greater numbers of immature neutrophils and classical monocytes, which represent dysregulated changes to the innate immune system that could predispose patients to an increased risk of secondary infection.[74]

Dysbiosis may lead to susceptibility to nosocomial infections caused by bacterial translocation. This concept is supported by observational evidence[75–78] describing associations between colonisation of the GI tract by the pathogenic *Enterococcus*,[75]

Table 3
Main phyla[a] of the human GI microbiota.

Actinomycetota	Gram-positive facultative anaerobes represented by Bifidobacteria genus; other examples are Corynebacterium, Nocardia, Actinomyces, and Mycobacterium
Firmicutes	Gram-positive aerobic and facultative anaerobic cocci and bacilli such as genera Enterococcus, Staphylococcus, Streptococcus, or Lactobacillus.
Proteobacteria	Gram-negative bacteria, e.g. pathogenic genera Escherichia, Klebsiella, Pseudomonas, Legionella, Acinetobacter, or Stenotrophomonas
Bacteroidota	Gram-negative anaerobes
Pseudomonodata	Enterobacteria that are anaerobic (and facultative anaerobic) gram-negative rods

[a] a phylum is one of seven hierarchical groups used to classify organisms (the broadest group after kingdom). Common gastrointestinal phyla in microbiota studies include Firmicutes, Bacteroidetes, Actinobacteria and Proteobacteria, the former two representing more than 90% of abundance. GI, gastrointestinal.

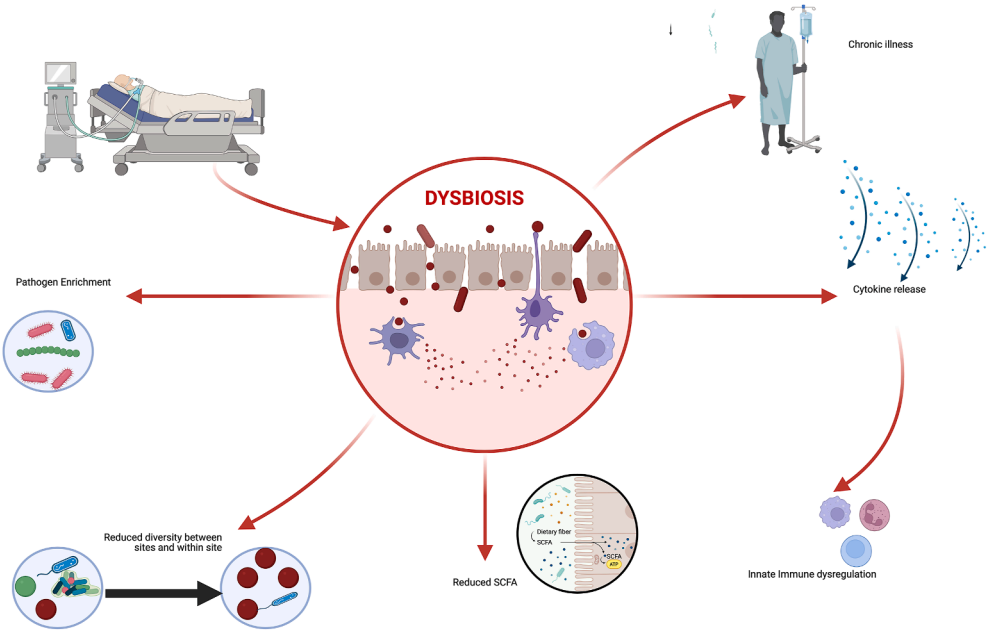

Fig. 4. Microbiome changes in critical illness and associated effects. Created in https://BioRender.com.

E. coli, Klebsiella, Enterobacter, Stenotrophomonas, and *Citrobacter* species,[76] and *Candida,*[78] and blood stream infections.

7.3. Importance of disease severity

There are a limited number of studies that report on the GI microbiome during critical illness.[79–82] There are even fewer studies that use modern next-generation sequencing methods to assess the changing microbiome.[65,83,84] Most studies included patients with an admitting diagnosis of sepsis (as defined by the sepsis II or III criteria) but not requiring mechanical ventilation (Table 4), and only a few studies (mostly case-control) have included mechanically ventilated patients[64,85–90] (Table 5). The absence of invasive mechanical ventilation is important because invasive mechanical ventilation is a crude measure of the severity of illness, i.e. more acutely unwell, critically ill patients will be invasively mechanically ventilated.[91]

7.4. Loss of diversity and richness and pathogen enrichment

The major findings from the above-mentioned studies were loss of diversity of the GI microbiota and an increased propensity to be colonised with potentially pathogenic taxa during and/or immediately following critical illness.

In one study 15 mechanically ventilated patients without prior comorbidities admitted after traumatic injury, out-of-hospital cardiac arrest, or an acute cerebrovascular event, 90% of their commensal intestinal microflora was lost within 6 h of ICU admission, with concurrent enrichment with *Enterococcus* and *Pseudomonas*.[92] Patients were excluded if they had previously received steroids or antibiotics.

In a single-centre case-control study, the microbiome of patients admitted to ICU following multitrauma injury or acute surgery was compared to those of healthy adults from the American Gut and Human Microbiome Project.[65] Similar to the previous study, alpha diversity was reduced from day 0 but remained stable; beta diversity was also significantly affected, and there was an enrichment of *Enterococcus* and depletion of *Faecalibacterium*, *Blautia*, and *Ruminococcus*. An observational study of 24 long-stay ICU patients (>5 days)[93] reported a reduction in diversity during admission. A recent observational study of patients with sepsis also reported a substantial decrease in the diversity and richness of GI microbiota.[94]

7.5. Timing of samples

The timing of stool collection in the ICU varies widely across studies. Two studies attempted to collect samples very early (6–24 h),[90,95] and most studies collected samples within two weeks of admission. One study collected samples as late as 50 days after admission.[85]

7.6. Dysbiosis over time

The duration for which GI dysbiosis persists following critical illness is unknown. One of the earliest studies with mechanically ventilated critically ill patients[96] reported a decrease in diversity of the GI microbiome and a proliferation of *Enterococcus* species with minimal recovery in those surviving ICU admission (followed up to 58 days). In a single-centre prospective cohort study of 191 patients undergoing elective cardiac surgery with a mean duration of mechanical ventilation of only 24 h,[97] and samples collected at admission, at a median of 4 days (IQR: 3–5 days) postadmission, and finally at a median of 71 days (IQR: 55–88 days) postadmission, the authors reported a trajectory of recovery of GI microbiota, although there remained a statistically significant difference between the last time point and prior to surgery. This study was also one of the first to obtain samples *prior* to hospital admission, which is very important because inter-individual differences in the microbiome profile mean that having a baseline for comparisons provides the best chance of detecting real differences (by definition, dysbiosis is relative). In a prospective trial across five mixed ICUs, faecal samples collected at two time points (within 72 h of admission and at discharge or day 10) from critically ill adults who were expected to remain mechanically ventilated for >72 h[88] reported a decrease in commensal bacteria (*Proteobacteria*) and an increase in taxa associated with inflammation (members of the Enterobacteriaceae family) at both time

Table 4
Summary of observational studies evaluating the gastrointestinal microbiome in critically ill patients who were not receiving mechanical ventilation.

Study	Study type	Sample size	Patient Cohort	Exclusion criteria	Illness severity/ admission diagnosis	Timing of sample collection	Control	GI Microbiome/Method of analysis
Magnan et al., 2023[91]	Prospective observational	60	Septic patients. (sepsis 3 criteria used)	Recent or scheduled GI surgery, exposure to laxatives, prebiotic or probiotic last 7 days, GI neoplasia, lymphoma, chronic IBD, moribund, pregnant or lactating	MV not reported. SOFA score 8.5 (7 −10). 28 day mortality 26.7%.	Day 0 and day 7 of ICU admission	100 healthy blood donors	Significant decrease in diversity and richness: Shannon score (2.97 at day 0 vs 2.63 at day 7; p = .0045) and Chao-1 score (102 at day 0 vs 86 at day 7; p = .0029) **16s rRNA amplicon sequencing**
Agudelo-Ochoa [78] et al., 2020	Case control	155 (septic = 72 nonseptic = 83), 250 samples.	Septic patients. (sepsis 3 criteria used)	<18 y, terminal illness, colostomy or ileostomy, pregnancy, homelessness	APACHE scores (sepsis group = 20.5 ± 7.6; nonseptic group = 16 ± 8.7), ICU LOS 6−10 days, 25% ICU mortality. MV − no information provided.	At ICU admission before nutritional support, then at day 5, 6, and 7 if the patient remained in ICU (44/72 septic patients),	Nonseptic ICU admissions	**Alpha diversity**: No difference. **Beta diversity:** Significantly different in sepsis (p = .013) **16S rRNA sequencing**
Ravi et al., 2019[90]	Prospective observational	24	Adults admitted in previous 72 h and expected to remain in ICU for next 48 h	n/a	Not reported; heterogenous population requiring ICU admission	Daily for first 5 days	n/a	Reduced diversity **Shotgun metagenomics**
Yeh et al., 2016[130]	Case control	32 patients, 79 samples	Trauma and acute surgical patients admitted to ICU	"Low quality samples" not otherwise specified.	Mean ICU LOS 8.8 days (1−24) Mean APACHE II score 12.6 (1−29) ISS mean 19.2 (4 −36) 88% required surgery.	Within 48 h of admission, then every 3−4 days three time periods were considered for analysis: (0−5 ICU days, 6−10 ICU days, >10 ICU days)	Samples from the American Gut Project and the Human Microbiome Project	**Alpha diversity:** Decreased at all time points. **Beta diversity:** Differed significantly from control. **Depletion of commensal** Faecalibacterium, Blautia, and Ruminococcus. **Enrichment** with enterococcus loss of site specificity and abundance of pathogenic taxa at three body sites simultaneously compared to healthy volunteers. **16s rRNA amplicon sequencing**
Zaborin et al., 2014[80]	Case series	14	Long stay patients (10 days to >30 days)	n/a	Severe sepsis (n = 2), GI bleed (n = 1), anaplastic astrocytoma (n = 1; only survivor) MV not specified	Several time points during the ICU admission	Five healthy volunteers not treated with antibiotics for 1 year prior to sample collection	Multiresistant ultra-low diversity microbiota and emergence of Candida albicans and glabrata in 75% of those samples. **16s rRNA amplicon sequencing**

ICU, intensive care unit; GI, gastrointestinal; APACHE, Acute Physiology and Chronic Health Evaluation.

Table 5
Summary of observational studies evaluating the gastrointestinal microbiome in critically ill patients who require mechanical ventilation.

Study	Study type	Sample size	Patient cohort	Exclusion criteria	Illness severity and mechanical ventilation	Timing of sample collection	Controls	GI microbiome/method of investigation
Zhang, 2022[81]	Case control	66	SARS-CoV-2 infected patients divided into four groups based on severity.	<18 y age Antibiotic or probiotic use in last 3 months	4 patients were mechanically ventilated	Of the 4 patients mechanically ventilated, 2 had stool samples after day 50 of illness; 1 patient at day 15, and 1 had 3 samples after day 15 and before day 40.	70 non-Covid controls Same exclusion criteria	The taxonomic composition significantly different to controls at a median of 28 days (IQR: 18−41). **Shotgun metagenomics**
Aardema, 2020[94]	Prospective observational	191 eligible patients.	Adult patients scheduled for CAGS and or valve surgery.	Lack of consent Physically unable to participate. Logistic reasons Acute admissions Non-ICU patients	APACHE IV 48[39–57] Euroscore 1.77 [1.07−2.91] Mean ICU LOS = 1d	Three time points: Preadmission on the day of preoperative screening; once during admission in the ICU or ward around day 4 (IQR: 3−5); and postadmission at a postdischarge routine visit or home visit on day 71 (IQR: 57−88).	nil	Significant increase in pathobionts; Decrease in strictly anaerobic gut bacteria; Lower bacterial diversity associated with longer hospitalisation. One of the very few studies that had follow-up after ICU discharge. **16S rRNA gene sequencing**
Lamarche, 2018[83] Canada	Prospective observational case control nested within an RCT (PROSPECT, NCT02462590)	34 ICU patients	Critically ill receiving MV	<18 y Received antibiotics in last 6 m immunocompromised GI compromise, Unable to receive enteral medications, pregnancy, end of life, Mechanical ventilation >72 h	APACHE 25.5 Median ICU LOS 11.5 (IQR 7, 20), ICU mortality 14.7%. Hospital mortality 35.3%. All on MV. Pneumonia 38.2%, sepsis 23%,	Stool samples were collected by a median of 6 days (IQR: 4.25−6.75). Study was nested in a randomised trial testing the probiotic L. rhamnosus GG versus placebo; to avoid confounding results due to probiotic administration, only samples collected in the first week were included. 21 healthy subject stool specimens were collected	Healthy donors enrolled in other studies[131–133]	Relative abundances of 29 OTUs for stool samples were significantly different between critically ill vs healthy individuals. OTUs from the Lachnospiraceae family, genera Faecalibacterium, Blautia, Subdoligranulum, and Lachnobacterium were depleted in stool specimens from ICU patients **16S rRNA gene sequencing**
Freedberg, 2018[92]	Prospective observational	301 patients	Adult patients admitted to a medical ICU via ED or from ward	n/a	MV 39.9% (n = 120) Reason for admission was “other” in 89%.	Routine rectal swabs at time of admission collected for VRE colonisation status were used		Fecal microbial diversity and richness were decreased in patients who were transferred to the ICU from a hospital ward compared to those admitted directly to the ICU (both $p < 0.01$) Diversity and richness were inversely correlated with the duration of pre-ICU hospitalisation (Spearman $p < 0.01$ for both) and were also inversely correlated with VRE colonisation and Enterococcus domination. Enterococcus dominance was more common in patients transferred to the

								ICU (20 vs 8%, $p < 0.01$) and those with a longer duration of pre-ICU hospitalisation (median difference + 11 days, $p < 0.01$); Neither fecal biodiversity (Shannon index) nor richness (Chao) differed between those who died or developed infections compared to those who did not ($p = 0.49$ and $p = 0.46$, respectively).
Lankelma, 2017[134]	Case control	34	All met ACCP/SCCM 1992 definition of sepsis, SIRS. All patients received SDD (polymyxin E, tobramycin, amphotericin B as an oral paste and IV cephalosporin)	Expected ICU LOS <24 h	APACHE IV score 83 (59−107), 80% were mechanically ventilated, 47% were shocked, admission diagnosis of sepsis in 74%.	One sample between 1 and 21 days of ICU admission.	15 healthy nonsmoking volunteers who had not had antibiotics for more than a year prior to faecal sampling	**16s rRNA gene sequencing** In 13 of the 34 patients, a single bacterial genus made up >50% of the gut microbiota. In 4 patients this was >75%; significant decrease in bacterial diversity in half of the patients. No associations between microbiota diversity, Firmicutes/Bacteroidetes ratio, or grampositive/ gram-negative ratio and complications and survival.
McDonald, 2016[85]	Case control	115	Mv and expected to remain on MV > 72 h	<18 y age	All mechanically ventilated	Two time points: within 72 h of admission and at discharge from ICU or day 10 in ICU.	Source samples using Qiita (healthy adults) from the American Gut Project	**16S rRNA sequencing** Significant rapid dysbiosis at <72 h that persisted and was worse at day 10.
Ojima 2015,[135]	Case control	12	ARDS, Head trauma, OHCA, sepsis Enteral nutrition was started within 48 h of admission	Postoperative patients with surgery of the rectum, patients with perianal infections, and patients expected to be on mechanical ventilation for <3 days,	All mechanically ventilated. APACHE 23.9 ± 12.4 SOFA 7.1 ± 4.1	Day 1−2, 2−4, 5−8, 7−10 after admission.	7 healthy subjects who had not been admitted to hospital or taken antibiotics in previous 6 m	**16S rRNA sequencing** Serial compositions of Bacteroidetes and Firmicutes changed significantly more in critically ill than in control from day 1 to day 10. Ratio of Bacteroidetes to Firmicutes changed significantly compared to controls in non-survivors.
Hayakawa, 2011[89]	Case control	15	Multiple trauma OHCA CVA Enteral nutrition.	<18 y Terminal illness Chronic disease-undefined Drug abuse	All were mechanically ventilated for a median of 5 days	Within 6 h of ICU admission And on days 1, 3, 5, 7, 10, and 14.	12 healthy volunteers	**16S rRNA sequencing** Significant drop in faecal floral counts on day 0 compared to controls. Obligate anaerobes and

(*continued on next page*)

Table 5 (*continued*)

Study	Study type	Sample size	Patient cohort	Exclusion criteria	Illness severity and mechanical ventilation	Timing of sample collection	Controls	GI microbiome/method of investigation
			No SDD, prebiotics or probiotics. IV antibiotics as indicated (Cefazolin, ceftriaxone, sulbactam/ cefoperazone, cefmetazole, piperacillin, meropenem, clindamycin, and amikacin)	Alcoholism Malnutrition nursing home resident On steroids or antibiotics Abdominal surgery	(IQR: 3−10). APACHE 21 (18 −26)			Lactobacillus, significantly decreased to one-thousandth in comparison to those of the control. Had not recovered at day 14. **Reverse transcription quantitative PCR (RT-qPCR)**
Iapichino 2008[93]	Observational	15	Acute organ failure requiring MV for >4 days	Hospital stay/antibiotic treatment prior to ICU, immunosuppression	All on MV Mean SOFA 6.2	Day of admission, then weekly.	nNl	Reduction in diversity of microbiota (less DGGE bands) and proliferation of Enterococcus. Denaturing gradient gel electrophoresis (DGGE)
Schlechte[69] 2023	Prospective observational	51	Patients >18 years of age admitted to ICU, requiring mechanical ventilation, and expected to require MV for >72 h	Pre-existing immunocompromised state, ICU admission or antimicrobial therapy the previous 3 months, had inflammatory bowel disease or active GI malignancy, previous surgery leaving a discontinuous GI tract, pregnancy, goals of care that excluded life-support interventions or moribund patients not expected to survive >72 h.	All on MV Median (IQR) SOFA score 8.0 (2−16) 30 day mortality 33.3% (17/51)	Day of admission, day 3 and 7	Healthy volunteers (n = 18)	Loss of Ruminococcaceaea and Lachnospiraceae and emergence of pathobiont taxa (Enterococcaceae and Enterobacteriaceae) 16s rRNA gene amplicon sequencing

ICU, intensive care unit; GI, gastrointestinal; APACHE, Acute Physiology and Chronic Health Evaluation; OTUs, operational taxonomic units.

points of collection, indicating rapid onset of dysbiosis in critical illness and failure of recovery at discharge from ICU. Another prospective cohort study of 25 patients with severe systemic inflammatory response syndrome (SIRS) reported a decrease in the commensal bacteria *Bifidobacterium* and *Lactobacillus* and an enrichment with pathogenic bacteria *Staphylococcus* and *Pseudomonas* compared to the stool samples of healthy volunteers.[81]

8. Relationship between GI microbial diversity, critical illness, and outcomes

Very few clinical studies have explored the relationship between GI dysbiosis and clinical outcomes during critical illness using newer culture-independent methods. Existing studies have included relatively small cohorts and have reported conflicting results. A prospective cohort study of 12 critically ill mechanically ventilated patients reported a modest relationship between the faecal Bacteriodetes to Firmicutes ratio (B/F ratio) and hospital mortality using 16S rRNA sequencing.[89] This ratio may be important because it provides a measure of the major commensal to pathobiont phyla in humans, although this relationship has not been found in other cohorts and has therefore been disputed. Another prospective study of 52 mechanically ventilated patients reported that dysbiosis, defined as the ratio of Enterobacteriaceae and Anaerococcus to Parasutterella and Campylobacter of >0 on the day of ICU admission, was associated with increased day-28 mortality compared to those with a ratio <0 (hazard ratio 2.2, 95% confidence interval, 1.1—4.3).[98]

Conversely, in a large prospective cohort study of 301 patients admitted to a medical ICU, routine admission rectal swabs for vancomycin-resistant *Enterococcus* surveillance were subjected to additional 16S rRNA sequencing. Patients were followed up for 30 days to investigate the association between admission GI microbiome and hospital mortality or culture-proven hospital-acquired infections.[95] There was no association between faecal biodiversity, as measured by the Shannon index, and richness, by Chao index, and either subsequent death or secondary infections. Similarly, a prospective study[87] of 34 patients did not identify an association between faecal microbiota diversity using the Firmicutes/Bacteroidetes ratio, and complications or survival.

It is likely that small sample sizes, heterogeneity of critical illness, older sequencing methodologies, and use of the F/B ratio as a marker of dysbiosis were some of the challenges in evaluating relationships between microbiota and outcomes. A recent meta-analysis concluded that there is currently insufficient evidence to link dysbiosis to ICU mortality.[63]

9. Relation between faecal short chain fatty acids and critical illness

SCFAs are by-products of saccharolytic fermentation of dietary fibres by anaerobic bacteria within the microbiota. In health, the 2—4 carbon atom SCFAs acetate, propionate, and butyrate are thought to be the most important. SCFAs are nutrients, absorbed in the colon and used by hepatocytes to synthesise fatty acids, and cholesterol, or are catabolised to produce glucose. SCFAs have been identified as key compounds in promoting intestinal integrity owing to their protective effect on barrier function, reduced bacterial translocation, improved mucous production and gut motility, and anti-inflammatory actions.[99] SCFA also stimulate the secretion of several important GI hormones, such as glucagon-like peptide-1.[100,101]

There is limited information regarding faecal SCFA concentrations in critically ill patients. A single-centre prospective cohort study of 15 patients admitted to ICU following out-of-hospital cardiac arrest, trauma, or stroke reported a reduction in faecal SCFA concentration within 6 h of initiation of mechanical ventilation.[90] Faecal SCFAs concentrations remained suppressed for the two weeks they were measured. Similarly, a prospective single-centre case-control trial comparing 140 patients meeting SIRS criteria (sepsis II) to 14 healthy volunteers[82] reported a substantial reduction in faecal SCFA production in critically ill patients compared to healthy controls, which was sustained for 6 weeks. A case-control study ($n = 25$) in patients meeting SIRS criteria reported reduced faecal SCFA concentrations compared to healthy volunteers.[81] Faecal sampling in these patients was performed at a mean of 9 ($\pm$7.4) days postadmission to ICU. In a post-hoc analysis, faecal SCFA concentrations were reduced in patients meeting SIRs criteria and in those who were feed-intolerant.[80] Similarly, in a randomised controlled trial, mechanically ventilated patients randomised to synbiotics had significantly higher faecal SCFA concentrations than the placebo group ($p < 0.05$).[102] In a case series of 5 patients with major burns, SCFA levels decreased to low levels initially but eventually increased in those that survived ($n = 4$) when measured at 43 (28—56) days.[79] Sepsis, as defined by the third consensus definition of sepsis, significantly reduced the faecal concentration of SCFAs compared to controls in a trial that enrolled 88 patients.[103] The mean Acute Physiology and Chronic Health Evaluation (APACHE) score in this study was 22 (IQR: 15—22) and the mortality was 27.3%.

While faecal SCFA concentrations rapidly reduce with the onset of critical illness, but the mechanism underlying this precipitous drop, whether it can be attenuated, and what the implications of this might be, remain to be elucidated. Because SCFAs are important for promoting intestinal integrity in health, interventions that increase SCFAs concentrations may have potential benefits for patient outcomes during critical illness.

Measuring faecal SCFA concentrations in ICU is challenging, as patients have long periods of nondefecation[104] and faecal concentration only quantifies net (production minus absorption) concentration excreted. These faecal excretion dynamics are relevant because SCFA production occurs in the proximal colon, but most SCFAs produced are absorbed by colonocytes, and only a minor proportion of the produced SCFA is excreted in faeces.[105] Accordingly, studies measuring faecal SCFA report the net result of production and absorption, not *in-situ* production rates.

Advances in metabolomics show promise in enabling identification of key interactions in metabolic pathways between host and the microbiome. This may help target interventions that enhance beneficial molecules, including SCFAs in the future.

10. Therapies to modify the gastrointestinal microbiota during critical illness

Potential interventions that have been studied to modulate the GI microbiota in health and disease include dietary fibre[106,107] and inulin[108] in particular, probiotics,[109,110] prebiotics,[111] synbiotics,[112–114] and adsorbent charcoal.[115] The role of dietary fibre in critical illness is summarised elsewhere.[116] Fibre-based enteral nutrition (EN) has shown the most promise in reversing critical illness-associated dysbiosis compared to supplementation of EN with symbiotics, omega-3 fatty acids, or arginine; however, the studies have been limited by small sample sizes and limited microbiome analytical methods. There is considerable recent interest in faecal microbiota transplantation (FMT) for chronic diseases because of its success in treating recurrent *Clostridioides difficile* infections.[117] Several case series have been conducted in patients with sepsis with mixed results.[118,119] The logistic barriers of acquiring appropriate transplant samples and administering them safely and in a timely fashion remain, as does the lack of

randomised trial evidence in critical illness (a pilot randomised controlled trial [RCT] to assess the safety of FMT in critical illness is planned[120]). The need to cease antibiotics prior to FMT is a limitation to the widespread use of FMT in this setting.[121]

11. Future directions

Mapping the human genome was considered to be an important step in understanding the human condition. With the realisation that there were more bacterial cells (10^{14}) than human body cells (10^{13}),[122,123] sequencing the genome of human microbiota became a priority. Despite the rapid technological and computational advances in metagenomics, several challenges remain.

The effect of gut dysbiosis on clinical outcomes in critical illness remains ill-defined.[63] Further large observational studies are required in this setting.[124] Microbiome assessments should be done more frequently in ICU research, and not be limited to the GI microbiome, particularly in mechanically ventilated patients with severe sepsis, multitrauma and post-solid-organ transplantation.

Interventions targeting microbiomes in critical illness are currently of increased interest, including selective digestive decontamination,[125,126] repopulating strategies using fibre, probiotics, prebiotics, symbiotics,[127–129] and faecal microbiota transplant[130–134] or its derived consortia and metabolites.

There is a growing realisation that viruses and fungi have an important role in the GI ecosystem. Future studies are required detailing these kingdoms and unpick their inter-kingdom interactions and role in immune regulation, infections, and outcomes in critical illness.

Methodological considerations and selective reporting in microbiome trials need addressing. The “Strengthening The Organization and Reporting of Microbiome Studies” (STORMS) checklist provides guidelines for concise and complete reporting. Epidemiological reporting guidelines such as the “Strengthening the Reporting of Observational studies in Epidemiology” (STROBE) have been adapted to metagenomics (STROBE-metagenomics).[135]

12. Conclusion

The translational goals of this emerging field are to establish mechanistic links between the microbiome and patient-important outcomes, seek interventions that might optimise outcomes, and design interventional studies powered to influence practice. The critical care clinician needs to be aware that while much remains unknown in this field, there is rapidly growing evidence that the human microbiome at various sites may have a profound effect on critical illness pathophysiology and outcome. Accordingly, interventions that favourably impact the readily accessible GI microbiome and/or metabolome (such as increased SCFAs) may lead to better patient outcomes.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix 1 (Search terms)

Microbiome:

phylogenetic profiling” or "microbial genome” or 16S or "microbial diversity” or "bacterial diversity” or dysbio* or disbio* or dysbacterio* or disbacterio* or "microbial composition” or "bacterial composition” or "gut flora” or microbiota or microbiom*

OR.

(Axis, Brain-Gut-Microbiome or Axis, Gut-Brain-Microbiome or Axis, Microbiome-Brain-Gut or Axis, Microbiome-Gut-Brain or Brain-Gut-Microbiome Axis or Fecal Microbiome Transplantation or Fecal Microbiome Transplantations or Fungal Microbiome or Gastric Microbiome or Gastrointestinal Microbiome or Gastrointestinal Microbiome or Gut Microbiome or Gut-Brain-Microbiome Axis or Human Microbiome or Intestinal Microbiome or Intestinal Microbiome Transfer or Intestinal Microbiome Transfers or Intestinal Microbiome Transplant or Intestinal Microbiome Transplantation or Intestinal Microbiome Transplantations or Intestinal Microbiome Transplants or Microbiome or Microbiome Brain Gut Axis or Microbiome Transfer, Intestinal or Microbiome Transfers, Intestinal or Microbiome Transplant, Intestinal or Microbiome Transplantation, Fecal or Microbiome Transplantation, Intestinal or Microbiome Transplantations, Fecal or Microbiome Transplantations, Intestinal or Microbiome Transplants, Intestinal or Microbiome, Fungal or Microbiome, Gastric or Microbiome, Gastrointestinal or Microbiome, Gut or Microbiome, Human or Microbiome, Intestinal or Microbiome, Viral or Microbiome, Virus or Microbiome-Gut-Brain Axis or Transfer, Intestinal Microbiome or Transfers, Intestinal Microbiome or Transplant, Intestinal Microbiome or Transplantation, Fecal Microbiome or Transplantation, Intestinal Microbiome or Transplantations, Fecal Microbiome or Transplantations, Intestinal Microbiome or Transplants, Intestinal Microbiome or Viral Microbiome or Virus Microbiome).mp.

Critical illness:

(Intensive care units or "critical care” or "critical illness” or "critically ill” or septic or sepsis or ARDS or "multiple organ failure” or ICU or shock or mechanical ventilation).mp. [mp = ti, ot, ab, fx, sh, hw, kw, tn, dm, mf, dv, kf, dq, bt, nm, ox, px, rx, an, ui, sy, ux, mx].

OR

Critical illness/or critical care/or exp intensive care units/or (ICU or ((intensive or critical) adj3 (care or unit*)) or (critical* adj3 ill*)).mp. or respiration, artificial/or (mechanical* adj3 ventilat*).mp. or (artificial* adj3 respiration*).mp.

OR

(((emergency or intensive or care) adj3 unit*) or ((critical* or acut*) adj (patient* or ill*))).ti,ab. or ICU.mp. or resuscitation.ti,ab. or exp intensive care unit/or exp critically ill patient/

OR

(Intensive care units or "critical care” or "critical illness” or "critically ill” or septic or sepsis or ARDS or "Mmltiple organ failure” or ICU or shock or mechanical ventilation).mp. [mp = title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms, population supplementary concept word, anatomy supplementary concept word].

SCFA

Fatty acids, volatile/or *acetates/or *butyrates/or *propionates/

Sequencing

Shotgun sequencing/or whole genome sequencing/(as a MESH term).

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